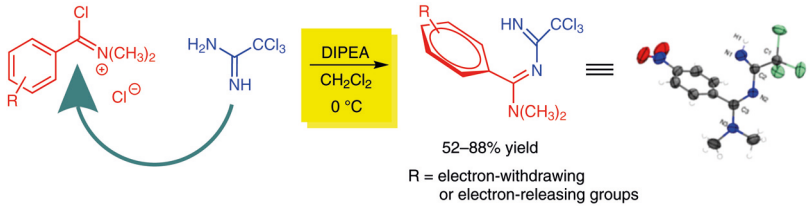
Synthesis A. Seballos-Resendiz et al. Paper

Synthesis and Crystal Structures of Stable 4-Aryl-2-(trichloromethyl)-1,3-diaza-1,3-butadienes

Arturo Seballos-Resendiz[a]
Harim Lechuga-Eduardo[a]
Joaquín Barroso-Flores[b]
Diego Martinez-Otero[b]
Moises Romero-Ortega*[a]

[a] Departamento de Química Orgánica, Facultad de Química, Universidad Autónoma del Estado de México Toluca, México, C.P. 50180
http://www.uaemex.mx/fquimica
mromeroo@uamex.mx
[b] Centro Conjunto de Investigación en Química Sustentable UAEM-UNAM, Toluca, México



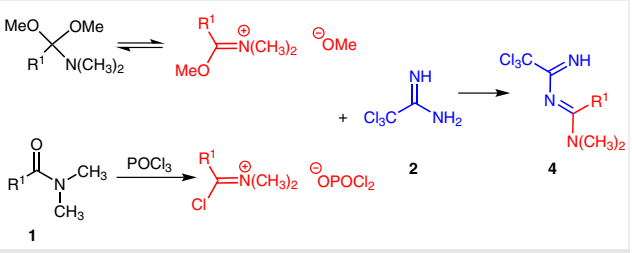
Received: 20.01.2016
Accepted after revision: 16.02.2016
Published online: 12.04.2016
DOI: 10.1055/s-0035-1561936; Art ID: ss-2016-m0028-op

Abstract A simple and convenient method to generate 4-aryl-substituted 1*H*-2-(trichloromethyl)-1,3-diaza-1,3-butadienes from aryl(chloro)methaniminium salts (best known as Vilsmeier–Haack reagents) and trichloroacetamidine has been developed. These 4-aryl-1*H*-1,3-diazabutadienes are isolable, relatively stable during silica gel chromatography, and can be crystallized. The analysis by X-ray diffraction demonstrated that in the solid state these 1,3-diazabutadienes have an *s-cisoid* conformation. The principal characteristic of these 1,3-diazabutadienes is their reactivity towards electron-deficient acetylenes, reacting under mild reaction conditions to produce 4-aryl-2-(trichloromethyl)pyrimidines in good yields.

Key words diazadienes, cycloaddition, nitrogen heterocycles, Vilsmeier–Haack reaction, coupling reactions, imines

1,3-Dienes containing one or two nitrogen atoms have attracted considerable attention in organic chemistry because of their potential utility in cycloaddition reactions for the construction of a wide variety of six-membered heterocycles.[1–3] Numerous examples of [4+2] cycloaddition reactions of simple conjugated azadienes and their 1,2- or 1,4-diaza-1,3-butadiene analogues have been published.[4–9] Although some 1,3-diazabutadienes have been used for [4+2] cycloaddition reactions,[10,11] the majority are of little value with regard to the generation of aromatic heterocyclic compounds.[12–14] The reason is that the 1- or *N*-substituent (aryl or alkyl group) makes the aromatization of the cycloadduct impossible. We became interested in the generation of 1-unsubstituted 1,3-diaza-1,3-butadienes with a dimethylamino group at the 4-position, since these 1,3-diazadienes can undergo [4+2] cycloaddition reactions with activated dienophiles such as acetylenic esters,[15] enamines,[11] and ketenes[16] to produce heterocyclic derivatives. In 1996 we reported a strategy to prepare 2-(trichloromethyl)-1,3-diaza-1,3-butadienes by using trichloroacetamidine and *N*,*N*-dimethylamide dimethyl acetals.[17] However, this methodology is limited by the use of the amide acetals.[18]

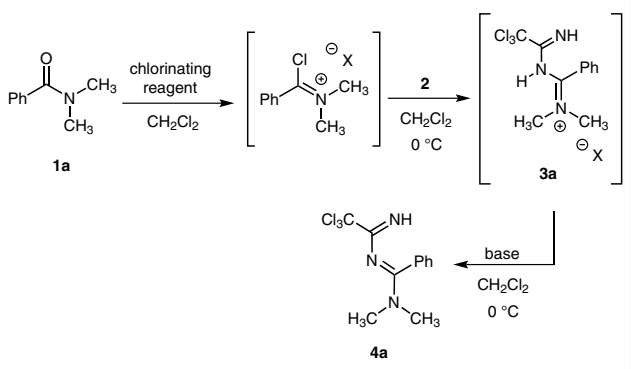
Although *N*,*N*-dimethylformamide (DMF) and *N*,*N*-dimethylacetamide (DMA) dimethyl acetals are commercially available, *N*,*N*-dimethylbenzamide dimethyl acetal is highly reactive and needs to be prepared from *N*,*N*-dimethylbenzamide before its use,[19] making the preparation of other *N*,*N*-dimethylarylamide acetal derivatives more difficult due to harsh reaction conditions and difficulty in scale-up.[20] In this context, amide acetals have been known to be powerful electrophilic reagents; their reactivity is largely due to the existence in solution of the corresponding iminium forms (Scheme 1). These ions are susceptible to attack at the central carbon by nucleophiles such as trichloroacetamidine to produce 1-unsubstituted 2-(trichloromethyl)-1,3-diazabutadienes.[21]



Scheme 1 Methaniminium salts as electrophilic species

We were concerned that this coupling process to produce 1,3-diaza-1,3-butadienes could be incompatible with the preparation of other 4-aryl congeners. As an alternative, it was thought that chloromethaniminium salts,[22] best known as Vilsmeier–Haack reagents,[23–25] might have potential for carbon–carbon bond-forming reactions and react in an analogous manner with amidines to give the corresponding 1*H*-1,3-diazadienes **4** (Scheme 1). However, aryl-

amidines and alkylamidines are stronger bases than ammonia (acetamidine pK_a = 12.4),[17] and they form well-crystallized salts as hydrochlorides. We have not yet found conditions to effect this reaction between amide acetals or chloromethaniminium salts with either amidines or their corresponding salts. Failure of the coupling reaction could be attributed to the basicity of these amidines. Trichloroacetamidine (**2**) is a much weaker base (pK_a = 6.5) and, fortunately, when *N*,*N*-dimethylbenzamide (**1a**) was converted into the corresponding Vilsmeier–Haack reagent by treatment with $POCl_3$, followed by coupling with amidine **2** (1 equiv), 4-phenyl-2-(trichloromethyl)-1,3-diaza-1,3-butadiene was formed as the corresponding salt **3a** (X = $OPOCl_2$) (Scheme 2).

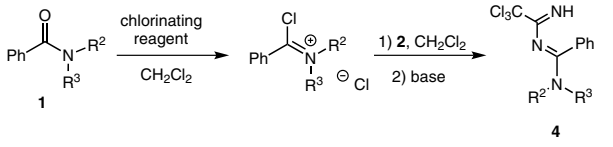


Scheme 2 Synthesis of 4-phenyl-2-(trichloromethyl)-1,3-diazadiene in the stable salt form **3a**

Our initial studies were based on the erroneous assumption that these 2-(trichloromethyl)-1,3-dienes **4** would be unstable in the free form, and that purification by column chromatography over silica gel might not be possible because of the tendency of **4** to undergo fragmentation reactions.[26] Therefore the liberation from its salt form **3** with a base was undertaken on the expectation that 4-phenyl-2-(trichloromethyl)-1,3-diaza-1,3-butadiene **4a** would be obtained in crude form. Fortunately, when this crude 1,3-diazadiene was purified by column chromatography, **4a** was obtained as a stable solid, and the best conditions for its generation were investigated (Table 1).

The reaction was carried out with one equivalent of chlorinating reagent and one equivalent of trichloroacetamidine (**2**). When $POCl_3$ was used as chlorinating reagent and Et_3N as a base, 4-phenyl-1,3-diazadiene **4a** was obtained, but in low yield (36%) (Table 1, entry 1). An attempt to generate this 1,3-diazadiene by using sodium acetate failed (entry 2) and produced *N*,*N*-dimethylbenzamidine as the only isolable product; this compound is suggested to arise as a consequence of partial fragmentation of 4-phenyl-1,3-diazabutadiene **4a**. The use of other bases such as DBU and 2,6-lutidine also resulted in poor yields of **4a** (entries 3 and 4). An improved yield was achieved by employ-

Table 1 Screening of the Generation of 1,3-Diazadiene **4**[a]



Entry	R^2, R^3	Chlorinating reagent	Base (equiv)	Yield (%)
1	CH_3, CH_3	$POCl_3$	Et_3N (5.0)	36 (**4a**)
2	CH_3, CH_3	$POCl_3$	AcONa (5.0)	–
3	CH_3, CH_3	$POCl_3$	DBU (5.0)	5 (**4a**)
4	CH_3, CH_3	$POCl_3$	2,6-lutidine (5.0)	8 (**4a**)
5	CH_3, CH_3	$POCl_3$	DIPEA (5.0)	74 (**4a**)
6	CH_3, CH_3	$(COCl)_2$	DIPEA (5.0)	88 (**4a**)
7	$(CH_2CH_2)_2O$	$(COCl)_2$	DIPEA (2.2)	75 (**4j**)

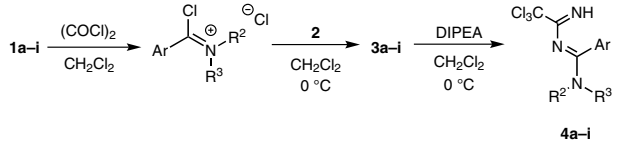
[a] Reaction conditions (see Scheme 2): 1. **1** (1 equiv), chlorinating reagent (1 equiv), anhyd CH_2Cl_2, r.t. to 35 °C, 5 h; 2. **2** (1 equiv), anhyd CH_2Cl_2, 0 °C to r.t., overnight; 3. base, anhyd CH_2Cl_2, 0 °C.

ing DIPEA as base (entry 5). We obtained an even higher yield when the chlorinating reagent was changed to oxalyl chloride and DIPEA (5.0 equiv) was used as base (entry 6). A decrease in the amount of the base (2.2 equiv) did not cause a substantial change in the yield of the compound **4a**. Although *N*,*N*-dimethylamides are often used in the formation of Vilsmeier–Haack reagents,[27] we found that when the amide was changed to a morpholide (entry 7), it gave a slightly lower yield of the product **4j**.

The methodology of the generation of 4-aryl-2-(trichloromethyl)-1,3-diazabutadienes **4** was extended. The Vilsmeier–Haack reagents were also prepared from the corresponding amides **1b**–**i** by using oxalyl chloride as chlorinating reagent and DIPEA as base; all these 4-aryl-1,3-diazabutadienes **4b**–**i**, as well as **4a**, were obtained as oils in their crude form (Table 2). However, in some cases, thin layer chromatography analysis showed that traces of the corresponding *N*,*N*-dialkylamide **1** were present in the product mixtures. A hallmark of these 4-aryl-1,3-diazadienes **4** is that they could be purified by column chromatography, and after purification could be obtained as crystals (except **4d** and **4f** that were isolated as oils) in good yields. To the best of our knowledge, this is the first time that these 1-unsubstituted 1,3-diazadienes could be obtained as crystals exhibiting prolonged stability at room temperature. We consider that these yields are respectable given that no intermediates were purified in the two-step reaction process beginning with the Vilsmeier–Haack reagent.

To further confirm the proposed structure, we obtained a single-crystal X-ray structure for compounds **4a**, **4c**, **4e**, **4g**, and **4h** (Figure 1). (See supporting information). Suitable single crystals were obtained from hexanes–dichloro-

Table 2 Synthesis of 4-Aryl-2-(trichloromethyl)-1,3-diazabutadienes **4a–i**[a]



Entry	R^2, R^3	Ar	4	Yield (%)	Mp (°C)
1	CH_3, CH_3	C_6H_5	**4a**	88	100–102
2	CH_3, CH_3	4-FC_6H_4	**4b**	70	67–69
3	CH_3, CH_3	4-$O_2NC_6H_4$	**4c**	69	132–134
4	CH_3, CH_3	3,4-$(CH_3)_2C_6H_3$	**4d**	59	oil
5	CH_3, CH_3	2-$CH_3C_6H_4$	**4e**	65	73–75
6	CH_3, CH_3	3,4-$(CH_3O)_2C_6H_3$	**4f**	66	oil
7	$(CH_2CH_2)_2O$	4-$CH_3OC_6H_4$	**4g**	52	93–95
8	$(CH_2CH_2)_2O$	4-ClC_6H_4	**4h**	54	106–109
9	$(CH_2CH_2)_2O$	4-$CH_3C_6H_4$	**4i**	63	122–125

[a] Reaction conditions: 1. **1** (1.0 equiv), $(COCl)_2$ (1.0 equiv), anhyd CH_2Cl_2, r.t. to 35 °C, 5 h; 2. **2** (1.0 equiv), anhyd CH_2Cl_2, 0 °C to r.t., overnight; 3. DIPEA (2.2 equiv), anhyd CH_2Cl_2, 0 °C.

methane mixtures. The compounds crystallized in the monoclinic system, the *P*2(1)/*c* space group for **4a**, **4e**, and **4g** and the *P*2(1)/*n* space group for **4c** and **4h**. The molecular structure indicates that in the solid state the aryl ring and the 1,3-diazabutadiene system have a dihedral angle C4–C5–C3–N2 ranging from 55.6(2) to 73.4(3)° that matches the calculated angle between the planes (plane 1: aromatic ring C4 to C9, plane 2: fragment N3–C3–N2) (Table 3). In theory, the 1,3-diaza-1,3-butadienes can exist in two isomeric forms with respect to the preferential arrangement of the substituents on N1 and C2.[28] Surprisingly, the X-ray structure shows that the conformations of the 1,3-diazabutadienes **4a**, **4c**, **4e**, **4g**, and **4h** are *s-cisoid* and that the geometry of the imine group (*s-cis* ***E*** and *s-cis* ***Z***) on N(1) depends on the nature of the substituent group on the aryl ring. When the aryl ring is substituted by an electron-donating group such as the methoxy group in **4g**, the interaction *s-cis* ***Z*** between N–H and the aromatic pi electron system becomes important. However, the direction of the N–H bond is not oriented towards the center of the aromatic ring. It can be seen that the distances between the hydrogen of the imine and the centroid calculated for the aromatic ring are relatively large: between 2.948–3.395 Å. In the case where the dihedral angle C2–N1–C1–H1 is close to 180°, the direction of the N–H bond is oriented towards the pi electrons of the C4–C9 bond of the aromatic ring, which is confirmed by the calculated bond distances to the centroid of the bond and are in the range of 2.62 to 2.74 Å. This conformation could possibly be favored because of hydrogen bonding of the NH group with the electron density of

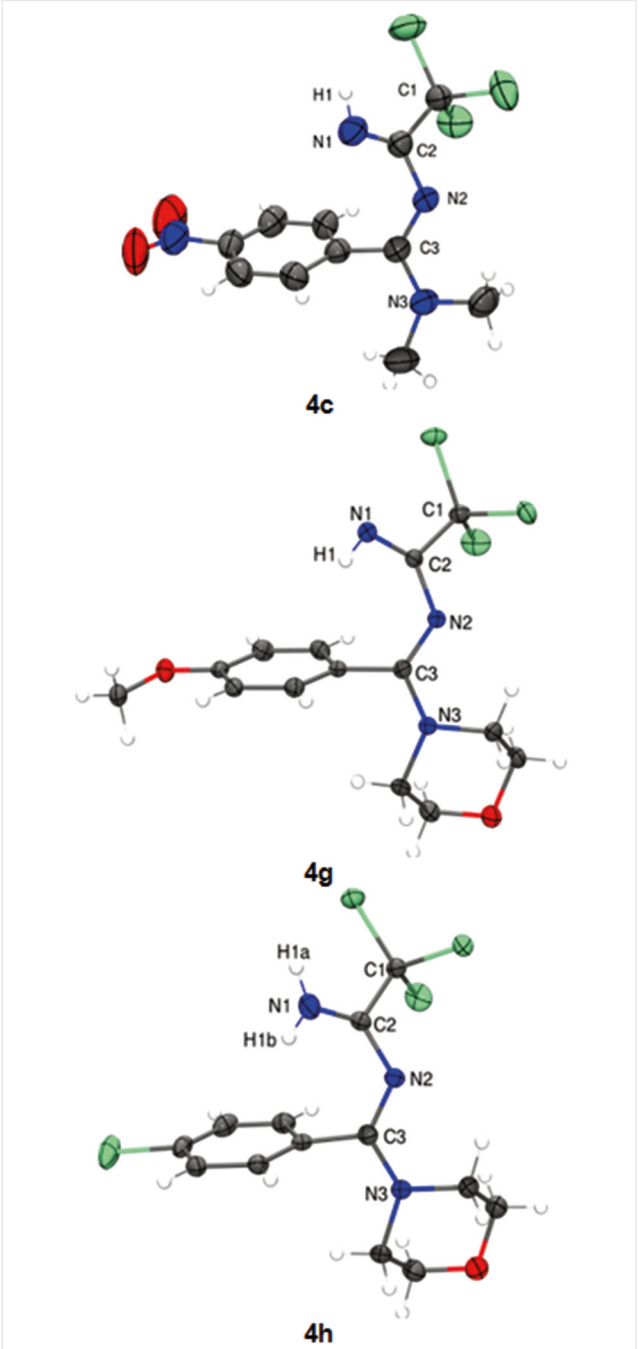


Figure 1 X-ray crystallographic structures of 1,3-diazabutadienes **4c**, **4g**, and **4h**

the pi bond C4–C9 which serves as a stabilizing force for this conformation. When the aryl ring is substituted by an electron-withdrawing group such as nitro in **4c**, the hydrogen of the NH group forms a hydrogen bond to the chlorine atom, with a distance H···Cl of 2.42(2) Å and an angle N1–H1···Cl2 of 123(2)°. In **4h** the aryl ring is substituted by a chlorine atom. The halogen is both electron-donating (by

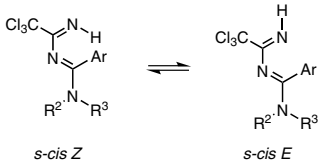
Table 3 Angles (°) and Distances (Å) Selected for **4a**, **4c**, **4e**, **4g**, and **4h**

	4a	4c	4e	4g	4h
Torsion angle N5–C4–C3–N2 (°)	72.7(2)	55.6(2)	73.4(3)	60.5(2)	65.1(2)
Angle between planes (plane 1: aromatic ring C4 to C9, plane 2: fragment N3–C3–N2) (°)	75.1	58.7	77.4	62.0	68.2
Torsion angle N1–C1–C2–H1 (absolute value, °)	179.4	4.8	171.6	175.0	3.1 (H1A) 178.6 (H1B)
Distance NH–centroid of ring C4 to C9 (Å)	3.291	4.065	3.395	3.100	4.039 (H1A) 2.948 (H1B)
Distance NH–centroid of bond C4–C9 (Å)	2.678	3.900	2.743	2.624	3.821 (H1A) 2.505 (H1B)

the resonance effect), and electron-withdrawing (by inductive effect), which results in positional disorder of the hydrogens on the NH group when **4h** is in the solid state. Two possible positions for the NH hydrogens were observed: in H1a, the hydrogen formed a hydrogen bond to the chlorine atom with a distance of 2.46(3) Å and an angle of N1–H1···Cl2 of 114(3)°. In H1b, the hydrogen interacts with the pi electrons of the aromatic ring with a distance of 2.51 Å. Each position (H1a and H1b) was assigned an occupancy of 0.5.

Also, relative energies were calculated for the *s-cis Z* and *s-cis E* conformations of the hydrogen atom on N-1 at the M06-2X/6-311++G (d,p) level of theory (Table 4). From these results it is readily observable that electron-donating groups such as the methoxy group in **4g** and the hydrogen atom itself in **4a** yield a slightly more stable *s-cis Z* conformation, whereas electron-withdrawing groups such as NO_2 in **4c** or Cl in **4h** favor the *s-cis E* conformation.

Table 4 Relative Energies for Compounds **4a**, **4c**, **4g**, and **4h** at the *s-cis Z* and *s-cis E* Conformations [kcal/mol]

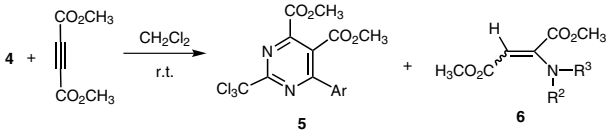


s-cis Z *s-cis E*

R^2, R^3	Ar	4	Relative energy [kcal/mol]	Most stable conformation
CH_3, CH_3	C_6H_5	**4a**	–1.31	*s-cis Z*
CH_3, CH_3	4-$O_2NC_6H_4$	**4c**	4.12	*s-cis E*
$(CH_2CH_2)_2O$	4-$CH_3OC_6H_4$	**4g**	–1.43	*s-cis Z*
$(CH_2CH_2)_2O$	4-ClC_6H_4	**4h**	1.13	*s-cis E*

As was expected, these 4-aryl-1,3-diazadienes **4** were very reactive in [4+2] cycloaddition reactions and reacted rapidly, even at room temperature, when they were treated with dimethyl acetylenedicarboxylate (DMAD) in CH_2Cl_2 (usually a exothermic reaction was observed) to give the 4-aryl-2-(trichloromethyl)pyrimidines **5a**–**i** in high yields (Table 5) accompanied by the dialkylamine–DMAD adduct **6**. Additionally, we have recently shown that these 2-(trichloromethyl)-1,3-diazabutadienes **4** also react with benzyne to give 4-substituted 2-(trichloromethyl)quinazolines through benzyne [4+2] cycloaddition,[26] and we have also found that they react with ketenes, results which will be published elsewhere.

Table 5 [4+2] Cycloaddition of 4-Aryl-1,3-diazabutadienes **4** with DMAD[a]



Entry	R^2, R^3	Ar	5	Yield (%)	mp (°C)
1	CH_3, CH_3	C_6H_5	**5a**	88	136–137
2	CH_3, CH_3	4-FC_6H_4	**5b**	85	124–125
3	CH_3, CH_3	4-$O_2NC_6H_4$	**5c**	96	118–119
4	CH_3, CH_3	3,4-$(CH_3)_2C_6H_3$	**5d**	82	140–141
5	CH_3, CH_3	2-$CH_3C_6H_4$	**5e**	52	74–75
6	CH_3, CH_3	3,4-$(CH_3O)_2C_6H_3$	**5f**	79	178–179
7	$(CH_2CH_2)_2O$	4-$CH_3OC_6H_4$	**5g**	77	157–158
8	$(CH_2CH_2)_2O$	4-ClC_6H_4	**5h**	86	139–140
9	$(CH_2CH_2)_2O$	4-$CH_3C_6H_4$	**5i**	85	153–154

[a] Reaction conditions: DMAD (2 equiv), **4** (1 equiv), anhyd CH_2Cl_2, r.t., 2–3 h.

In summary, we have developed an efficient methodology for the preparation and isolation of 4-aryl-2-(trichloromethyl)-1,3-diaza-1,3-butadienes from Vilsmeier–Haack reagents and trichloroacetamidine. The hallmark of these 4-aryl-1,3-diaza-1,3-butadienes is that they were isolated. Density functional calculations show the changes in the electrostatic potential of the hydrogen atom on N-1 and how they direct the final conformation to either *s-cis E* or *s-cis Z* depending on the electron-withdrawing capacities of the various functional groups.

All moisture-sensitive reactions were carried out in oven-dried glassware under an argon atmosphere. Reagents were purchased from Aldrich and used without any further purification. Trichloroacetamidine was prepared from trichloroacetonitrile according to a published procedure.[29] CH_2Cl_2 was distilled from CaH_2 under argon. NMR spectra were recorded at 300 MHz (^{1}H NMR) on a Bruker Avance 300 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm) relative to Me_4Si (δ = 0.0 ppm). ^{13}C NMR signals are reported relative to $CDCl_3$ (δ = 77.0 ppm) as internal reference. Melting points were measured in a Mel-Temp II apparatus and are uncorrected. Mass spectra were recorded on a Shimadzu GCMS-QP2010 plus (EI, 70 eV).

Crystallography Data[30]

Data for **4a**, **4c**, **4e**, **4g** and **4h** were collected on a Bruker APEX II CCD diffractometer at 100 K for **4a**, **4g**, and **4h** and 273 K for **4c** and **4e**, using Mo-Kα radiation (k = 0.71073 Å) from an Incoatec ImuS source and Helios optic monochromator. Suitable crystals of **4c** and **4e** were glued to a glass fiber and mounted in the diffractometer, whereas in the case of **4a**, **4g**, and **4h** the crystals were coated with hydrocarbon oil, picked up with a nylon loop, and mounted in the cold nitrogen stream of the diffractometer. The structures were solved by direct methods (SHELXS-97) and refined by full-matrix least-squares on $F2$ using the shelXle GUI. The hydrogen atoms of the C–H bonds were placed in idealized positions whereas the hydrogen atoms of the N–H moieties were localized from the difference electron density map, and their position was refined with U_{iso} tied to the parent atom with distance restraints. The hydrogen of the N–H group in **4h** present positional disorder in two positions; the hydrogens were localized from the difference electron density map and assigned occupancy of 0.5 for H1A and H1B. The disordered aryl group in **4e** was refined using geometry and distance restraints (SAME, SADI) together with the restraints for the U_{ij} values (SIMU, RIGU) implemented in SHELXL; the occupancy for the majority position is 0.863(3) and the occupancy for the second positions is 0.137(3). The molecular graphics were prepared using ORTEP, POV-RAY, and GIMP.

Computational Details

Single point calculations were carried out with the use of the Gaussian09 suite of programs at the M06-2X/6-311++G(*d*,*p*) level of theory with the crystal geometries as input structures. Orbital populations were analyzed under the Natural Bond Orbital (NBO) formalism as implemented in the NBO3.1 program supplied with the aforementioned suite.

4-Aryl-4-(dialkylamino)-2-(trichloromethyl)-1,3-diaza-1,3-butadienes 4; General Procedure

Oxalyl chloride (1.0 equiv) was added dropwise at r.t. (except in synthesis of **4e**, where addition was at 0 °C) to the corresponding *N*,*N*-dialkylbenzamide **1** (1.0 equiv) in anhydrous CH_2Cl_2 (1.0 mL/mmol **1**) under N_2 atmosphere. The reaction mixture was heated at 35 °C for 5 h. Generally, a white solid was observed after few minutes. When the reaction was finished, anhydrous CH_2Cl_2 was added (4.0 mL/mmol **1**) at 0 °C; usually at this temperature the solid dissolved. A solution of trichloroacetamidine **2** (1.0 equiv) in anhydrous CH_2Cl_2 (1.0 mL/mmol **2**) was added dropwise at 0 °C. Immediately a white suspension formed, and the reaction mixture was stirred overnight at r.t. Finally, DIPEA (2.2 equiv) was added at 0 °C; a pale yellow solution resulted. CH_2Cl_2 (20 mL) was added and the organic phase was washed with saturated NaCl solution, dried over Na_2SO_4, and concentrated in vacuo. The resulting crude 1,3-diazabutadiene **4** was obtained in quantitative yield, usually contaminated with small quantities of starting material as an oil that slowly crystallized. The 1,3-diazadienes **4** were purified by flash column chromatography (silica gel, hexanes–EtOAc). After purification, 1,3-diazadienes **4** were obtained as crystals or as oils.

4-(Dimethylamino)-4-phenyl-2-(trichloromethyl)-1,3-diaza-1,3-butadiene (4a)

From **1a** (540 mg, 3.6 mmol), **4a** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 65:35).

Yield: 940 mg (88%); white solid; crystallization (EtOAc); mp 100–102 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (s, 5 H), 3.21 (s, 3 H), 2.87 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.19, 165.10, 131.74, 130.05, 128.59, 127.85, 96.94, 39.99, 38.31.

MS: m/z (%) = 294 (11) [M^+ + 4], 292 (25) [M^+ + 2], 290 (22) [M^+], 174 (67), 104 (49), 77 (100), 71 (46), 44 (67).

4-(Dimethylamino)-4-(4-fluorophenyl)-2-(trichloromethyl)-1,3-diaza-1,3-butadiene (4b)

From **1b** (390 mg, 2.3 mmol), **4b** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 7:3, then 65:35).

Yield: 500 mg (70%); white solid; crystallization (EtOAc); mp 67–69 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.33 (m, 2 H), 7.14–7.08 (m, 2 H), 3.23 (s, 3 H), 2.86 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.29, 164.83, 163.12, 161.52, 129.74, 129.63, 128.23, 128.18, 115.88, 115.59, 97.51, 39.56, 37.83.

MS: m/z (%) = 312 (38) [M^+ + 4], 310 (82) [M^+ + 2], 308 (68) [M^+], 193 (33), 136 (44), 123 (50), 122 (100), 121 (31), 95 (70), 75 (29), 44 (66).

4-(Dimethylamino)-4-(4-nitrophenyl)-2-(trichloromethyl)-1,3-diaza-1,3-butadiene (4c)

From **1c** (450 mg, 2.3 mmol), **4c** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 65:35, then 6:4).

Yield: 539 mg (69%); white solid; crystallization (EtOAc); mp 132–134 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.28 (d, J = 9.0 Hz, 2 H), 7.56 (d, J = 9.0 Hz, 2 H), 3.28 (s, 3 H), 2.85 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.53, 161.69, 148.26, 138.86, 131.07, 128.94, 123.56, 123.44, 96.97, 39.47, 37.84.

MS: m/z (%) = 339 (4) [M^+ + 4], 337 (10) [M^+ + 2], 335 (11) [M^+], 219 (69), 173 (37), 91 (51), 71 (53), 57 (44), 44 (100), 43 (78), 41 (46).

4-(Dimethylamino)-4-(3,4-dimethylphenyl)-2-(trichloromethyl)-1,3-diaza-1,3-butadiene (4d)

From **1d** (619 mg, 3.5 mmol), **4d** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 65:35).

Yield: 660 mg (59%); oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17 (d, J = 9.0 Hz, 1 H), 7.09 (d, J = 9.0 Hz, 1 H), 7.05 (s, 1 H), 3.21 (s, 3 H), 2.86 (s, 3 H), 2.26 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.89, 164.52, 138.47, 137.09, 129.88, 129.59, 128.43, 124.92, 97.97, 39.58, 37.74, 19.83, 19.72.

4-(Dimethylamino)-4-(2-methylphenyl)-2-(trichloromethyl)-1,3-diaza-1,3-butadiene (4e)

From **1e** (380 mg, 3.5 mmol), **4e** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 7:3).

Yield: 460 mg (65%); white solid; crystallization (hexanes–CH_2Cl_2); mp 73–75 °C (EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.19 (m, 4 H), 3.28 (s, 3 H), 2.77 (s, 3 H), 2.31 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.92, 163.80, 135.74, 132.53, 130.00, 129.41, 126.47, 126.09, 97.93, 38.29, 37.24, 19.42.

MS: *m*/*z* (%) = 308 (12) [M^+ + 4], 306 (17) [M^+ + 2], 304 (9) [M^+], 290 (62), 188 (99), 118 (43), 91 (30), 71 (100), 65 (20), 44 (31).

4-(3,4-Dimethoxyphenyl)-4-(dimethylamino)-2-(trichloromethyl)-1,3-diaza-1,3-butadiene (4f)

From **1f** (483 mg, 2.3 mmol), **4f** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 1:1).

Yield: 540 mg (66%); oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.92–6.89 (m, 3 H), 3.90–3.85 (m, 6 H), 3.21–2.92 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.17, 153.28, 150.07, 149.12, 120.73, 110.82, 110.63, 110.17, 97.88, 56.00, 55.84, 39.69, 37.88.

4-(4-Methoxyphenyl)-4-morpholino-2-(trichloromethyl)-1,3-diaza-1,3-butadiene (4g)

From **1g** (520 mg, 2.3 mmol), **4g** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 65:35).

Yield: 260 mg (52%); white solid; crystallization (EtOAc); mp 93–95 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (d, *J* = 9.0 Hz, 2 H), 6.94 (d, *J* = 9.0 Hz, 2 H), 3.82 (m, 11 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.69, 163.25, 160.74, 132.35, 129.23, 123.23, 114.21, 113.53, 97.42, 66.74, 55.28, 48.12.

MS: *m*/*z* (%) = 366 (14) [M^+ + 4], 364 (33) [M^+ + 2], 362 (31) [M^+], 246 (76), 135 (100), 134 (89), 77 (32).

4-(4-Chlorophenyl)-4-morpholino-2-(trichloromethyl)-1,3-diaza-1,3-butadiene (4h)

From **1h** (520 mg, 2.3 mmol), **4h** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 65:35).

Yield: 460 mg (54%); crystals; crystallization (EtOAc); mp 106–109 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.30 (m, 4 H), 3.78–3.22 (m, 8 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.03, 161.93, 136.04, 129.73, 129.16, 129.00, 96.99, 66.65, 45.65.

MS: *m*/*z* (%) = 370 (16) [M^+ + 4], 368 (31) [M^+ + 2], 366 (24) [M^+], 252 (34), 250 (100), 140 (29), 139 (75), 138 (76), 113 (30), 111 (44), 86 (30), 75 (29), 69 (45), 44(35).

4-(4-Methylphenyl)-4-morpholino-2-(trichloromethyl)-1,3-diaza-1,3-butadiene (4i)

From **1i** (479 mg, 2.3 mmol), **4i** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 65:35).

Yield: 500 mg (63%); crystals; crystallization (hexanes–CH_2Cl_2); mp 122–125 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.23 (s, 4 H), 3.78–3.24 (m, 8 H), 2.37 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.60, 163.34, 140.13, 129.49, 128.32, 127.53, 97.41, 66.74, 47.88, 45.27, 21.42.

MS: *m*/*z* (%) = 350 (22) [M^+ + 4], 348 (49) [M^+ + 2], 346 (43) [M^+], 230 (96), 119 (43), 118 (100), 91 (46), 69 (29), 42 (22).

6-Aryl-2-(trichloromethyl)pyrimidines 5; General Procedure

DMAD (2.0 equiv) was added dropwise to a stirred solution of 1,3-diazabutadiene **4** in anhydrous CH_2Cl_2 (1mL/mmol **4**) under N_2 atmosphere at r.t. (usually an exothermic reaction was observed) and the reaction mixture was stirred 2–3 h. After this time, two products were observed by TLC analysis (**5** and the addition product of the corresponding dialkylamine to DMAD). CH_2Cl_2 (20 mL) was added and the organic phase was washed with saturated NaCl solution, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes–EtOAc); this gave **5**.

Dimethyl 6-Phenyl-2-(trichloromethyl)pyrimidine-4,5-dicarboxylate (5a)

From **4a** (530 mg, 1.8 mmol), **5a** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 9:1).

Yield: 622 mg (88%); white solid; crystallization (CH_2Cl_2–hexanes); mp 136–137 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84–7.81 (m, 2 H), 7.57–7.52 (m, 3 H), 4.05 (s, 3 H), 3.87 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.33, 166.30, 165.22, 163.74, 155.10, 135.48, 131.60, 128.96, 125.28, 95.68, 53.89, 53.40.

MS: *m*/*z* (%) = 392 (5) [M^+ + 4], 390 (16) [M^+ + 2], 388 (17) [M^+], 353 (89), 272 (47), 142 (63), 127 (70), 59 (100).

Dimethyl 6-(4-Fluorophenyl)-2-(trichloromethyl)pyrimidine-4,5-dicarboxylate (5b)

From **4b** (320 mg, 1.0 mmol), **5b** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 9:1).

Yield: 360 mg (85%); white solid; crystallization (CH_2Cl_2–hexanes); mp 124–125 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88–7.83 (m, 2 H), 7.24–7.19 (m, 2 H), 4.06 (s, 3 H), 3.96 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = ($CDCl_3$) 166.61, 166.28, 165.21, 165.08, 163.66, 155.14, 131.40, 131.28, 125.08, 116.43, 116.14, 95.58, 53.96, 53.53.

MS: *m*/*z* (%) = 410 [M^+ + 4], 408 (16) [M^+ + 2], 406 (16) [M^+], 371 (42), 292 (50), 290 (52), 59 (100).

Dimethyl 6-(4-Nitrophenyl)-2-(trichloromethyl)pyrimidine-4,5-dicarboxylate (5c)

From **4c** (290 mg, 0.85 mmol), **5c** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 9:1).

Yield: 350 mg (96%); white solid; crystallization (CH_2Cl_2–hexanes); mp 118–119 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.38 (d, *J* = 9 Hz, 2 H), 7.98 (d, *J* = 9 Hz, 2 H), 4.08 (s, 3 H), 3.90 (s, 3 H), 2.34 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.55, 164.17, 163.35, 155.68, 149.52, 141.10, 130.13, 125.67, 124.04, 95.26, 54.12, 53.79.

MS: *m*/*z* (%) = 437 (3) [M^+ + 4], 435 (7) [M^+ + 2], 433 (6) [M^+], 398 (85), 368 (83), 317 (88), 59 (100).

Dimethyl 6-(3,4-Dimethylphenyl)-2-(trichloromethyl)pyrimidine-4,5-dicarboxylate (5d)

From **4d** (390 mg, 1.2 mmol), **5d** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 9:1).

Yield: 590 mg (82%); a solid; crystallization (CH_2Cl_2–hexanes); mp 140–141 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62–7.53 (m, 2 H), 7.27–7.24 (m, 1 H), 4.04 (s, 3 H), 3.89 (s, 3 H), 2.34 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.56, 166.39, 165.09, 163.85, 154.87, 141.10, 137.54, 133.03, 130.23, 130.10, 126.39, 124.98, 95.80, 53.84, 53.30, 19.89, 19.86.

MS: *m*/*z* (%) = 420 (31) [M$^+$ + 4], 418 (83) [M$^+$ + 2], 416 (83) [M$^+$], 382 (100), 380 (85), 140 (73).

Dimethyl 6-(2-Methylphenyl)-2-(trichloromethyl)pyrimidine-4,5-dicarboxylate (5e)

From **4e** (220 mg, 1.1 mmol), **5e** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 95:5).

Yield: 230 mg (52%); white solid; crystallization (CH_2Cl_2–hexanes); mp 74–75 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.26 (m, 4 H), 4.06 (s, 3 H), 3.70 (s, 3 H), 2.31 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.95, 165.41, 164.80, 163.69, 154.78, 136.84, 134.82, 131.16, 130.43, 128.41, 126.89, 125.70, 95.65, 53.92, 53.19, 19.89.

MS: *m*/*z* (%) = 406 (2) [M$^+$ + 4], 404 (4) [M$^+$ + 2], 402 (4) [M$^+$], 345 (98), 343 (100), 247 (87), 59 (79).

Dimethyl 6-(3,4-Dimethoxyphenyl)-2-(trichloromethyl)pyrimidine-4,5-dicarboxylate (5f)

From **4f** (406 mg, 1.1 mmol), **5f** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 9:1).

Yield: 408 mg (79%); yellow solid; crystallization (CH_2Cl_2–hexanes); mp 178–179 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (m, 2 H), 6.97 (m, 1 H), 4.05–3.92 (m, 12 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.84, 165.35, 164.96, 163.84, 154.87, 152.33, 149.36, 127.89, 124.63, 122.78, 111.88, 111.14, 56.07, 55.99, 53.88, 53.47.

MS: *m*/*z* (%) = 454 (14) [M$^+$ + 4], 452 (99) [M$^+$ + 2], 450 (89) [M$^+$], 447 (34), 413 (52), 59 (100).

Dimethyl 6-(4-Methoxyphenyl)-2-(trichloromethyl)pyrimidine-4,5-dicarboxylate (5g)

From **4g** (310 mg, 0.85 mmol), **5g** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 9:1).

Yield: 270 mg (77%); white solid; crystallization (CH_2Cl_2–hexanes); mp 157–158 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 9 Hz, 2 H), 7.01 (d, *J* = 9 Hz, 2 H), 4.04 (s, 3 H), 3.91 (s, 3 H), 3.89 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.76, 165.42, 165.00, 163.90, 162.67, 154.98, 130.93, 127.73, 124.40, 114.51, 95.83, 55.48, 53.83, 53.40.

MS: *m*/*z* (%) = 422 (28) [M$^+$ + 4], 420 (81) [M$^+$ + 2], 418 (82) [M$^+$], 383 (66), 59 (100).

Dimethyl 6-(4-Chorophenyl)-2-(trichloromethyl)pyrimidine-4,5-dicarboxylate (5h)

From **4h** (216 mg, 0.6 mmol), **5h** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 9:1).

Yield: 213 mg (86%); white solid; crystallization (CH_2Cl_2–hexanes); mp 139–140 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.79–7.76 (m, 2 H), 7.52–7.49 (m, 2 H), 4.06 (s, 3 H), 3.89 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.15, 165.29, 165.06, 163.61, 155.24, 138.30, 133.82, 130.33, 129.34, 125.16, 95.54, 53.98, 53.58.

MS: *m*/*z* (%) = 428 (2) [M$^+$ + 6], 426 (10) [M$^+$ + 4] 424 (20) [M$^+$ + 2], 422 (15) [M$^+$], 139 (100), 111 (43), 59 (83).

Dimethyl 6-(4-Methylphenyl)-2-(trichloromethyl)pyrimidine-4,5-dicarboxylate (5i)

From **4i** (350 mg, 1,0 mmol), **5i** was obtained after purification by flash column chromatography (silica gel, hexanes–EtOAc, 9:1).

Yield: 347 mg (85%); white solid; crystallization (CH_2Cl_2–hexanes); mp 153–4 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (d, *J* = 9.0 Hz, 2 H), 7.32 (d, *J* = 9.0 Hz, 2 H), 4.05 (s, 3 H), 3.89 (s, 3 H), 2.44 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.54, 166.19, 165.12, 163.83, 154.97, 142.39, 132.66, 129.76, 128.96, 124.96, 95.75, 53.89, 53.41, 21.53.

MS: *m*/*z* (%) = 406 (19) [M$^+$ + 4], 404 (52) [M$^+$ + 2], 402 (52) [M$^+$], 369 (88), 367 (100), 286 (60), 140 (74), 59 (94).

Acknowledgment

Financial support for this research was provided by CONACYT and DGAPA–UNAM grant IB2003-13 and is gratefully acknowledged. The authors wish to thank M. Sc. Maria de las Nieves Zabala Segovia (CCIQS UNAM-UAEM) for obtaining the NMR analysis and DGCTIC–UNAM for access granted to the supercomputing facility. Also to Professor Joseph M. Muchowski from the UNAM for helpful discussions and his interest in our work.

Supporting Information

Supporting Information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561936.

References

(1) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869.
(2) Boger, D. L.; Kasper, A. M. *J. Am. Chem. Soc.* **1989**, *111*, 1517.
(3) Jayakumar, S.; Ishar, M. P. S.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379.
(4) Boeckman, R. K.; Reed, J. E.; Ge, P. *Org. Lett.* **2001**, *3*, 3651.
(5) Boeckman, R. K.; Ge, P.; Reed, J. E. *Org. Lett.* **2001**, *3*, 3647.
(6) Avalos, M.; Babiano, R.; Cintas, P.; Clemente, F. R.; Jiménez, J. L.; Palacios, J. C.; Sánchez, J. B. *J. Org. Chem.* **1999**, *64*, 6297.
(7) Lorenz, V.; Hrib, C. G.; Grote, D.; Hilfert, L.; Krasnopolski, M.; Edelmann, F. T. *Organometallics* **2013**, *32*, 4636.
(8) Trifonov, A. A.; Shestakov, B. G.; Lyssenko, K. A.; Larionova, J.; Fukin, G. K.; Cherkasov, A. V. *Organometallics* **2011**, *30*, 4882.
(9) Tronnier, A.; Pöthig, A.; Metz, S.; Wagenblast, G.; Münster, I.; Strassner, T. *Inorg. Chem.* **2014**, *53*, 6346.

(10) Nandy, M. S.; Sharma, M.; Pal, M. M. *Tetrahedron Lett.* **1987**, *28*, 2641.
(11) Barluenga, J.; Tomás, M.; Ballesteros, A.; López, L. A. *Tetrahedron Lett.* **1989**, *30*, 4573.
(12) Burger, K.; Penninger, S. *Synthesis* **1978**, 524.
(13) Abbiati, G.; Contini, A.; Nava, D.; Rossi, E. *Tetrahedron* **2009**, *65*, 4664.
(14) Dalla Croce, P.; Ferraccioli, R.; La Rosa, C. *Heterocycles* **1997**, *45*, 9.
(15) Ibnusaud, I.; Padma Malar, E. J.; Sundaram, N. *Tetrahedron Lett.* **1990**, *31*, 7357.
(16) Luthardt, P.; Würthwein, E.-U. *Tetrahedron Lett.* **1988**, *29*, 921.
(17) Guzmán, A.; Romero, M.; Talamás, F. X.; Villena, R.; Greenhouse, R.; Muchowski, J. M. *J. Org. Chem.* **1996**, *61*, 2470.
(18) Salomon, R. G.; Raychaudhuri, S. R. *J. Org. Chem.* **1984**, *49*, 3659.
(19) Hanessian, S.; Moralioglu, E. *Can. J. Chem.* **1972**, *50*, 233.
(20) Usually, amide dimethyl acetals are prepared from the corresponding *N*,*N*-dimethylamide and dimethyl sulfate followed by treatment with sodium methoxide; by using this methodology, the *N*,*N*-dimethylbenzamide dimethyl acetal can be obtained in low yield (44%) and usually contaminated with *N*,*N*-dimethylbenzamide or/and methyl benzoate.
(21) Muzart, J. *Tetrahedron* **2009**, *65*, 8313.
(22) Marson, C. M.; Giles, P. R. *Synthesis Using Vilsmeier Reagents (New Directions in Organic & Biological Chemistry)*, 1st ed.; CRC Press: Boca Raton, Florida, **1994**.
(23) Kumar, A. S.; Nagarajan, R. *Org. Lett.* **2011**, *13*, 1398.
(24) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2002**, *4*, 553.
(25) Majo, V. J.; Perumal, P. T. *Tetrahedron Lett.* **1996**, *37*, 5015.
(26) Lechuga-Eduardo, H.; Olivo, H. F.; Romero-Ortega, M. *Eur. J. Org. Chem.* **2014**, 5910.
(27) White, J.; McGillivray, G. *J. Org. Chem.* **1977**, *42*, 4248.
(28) Bharatam, P. V.; Kumar, R. S.; Mahajan, M. P. *Org. Lett.* **2000**, *2*, 2725.
(29) Albert, A.; Paal, B. *Chem. Ind. (London)* **1974**, 874.
(30) CCDC 1430285 (**4a**), 1430286 (**4c**), 1430287 (**4e**), 1430288 (**4g**), 1430289 (**4h**). contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.